Title : FENTANYL PHARMACOKINETICS IN MAN

Authors : D.A. McClain, M.D. and C.C. Hug, Jr., M.D., Ph.D.

Affiliation: Department of Anesthesiology, Emory University Medical School
Atlanta, Georgia 30322

INTRODUCTION. Fentanyl (F) is considered to be a "short-acting" narcotic analgesic. However, prolonged and recurrent ventilatory depression has been reported in man. Studies in dogs suggest that the short duration of F action after single moderate doses is due to its rapid redistribution from brain to other tissues and that repeated or large doses lead to accumulation of F and ventilatory depression.[1,2] This study examined the pharmacokinetics of F in man in order to determine the applicability of conclusions from animal studies to humans.

METHODS. Six normal males (22-29 yrs) gave informed consent to this institutionally approved study. They weighed 65-85 kg, fasted before and during the study, received iv fluids (2 ml/kg/hr), and breathed O_2 for 45 min after fentanyl injection. Respiration, blood gases, blood pressure, ECG, and urine output were monitored. A 5 or 10 μg/kg dose of ^{3}H-fentanyl citrate (87 nCi/μg) was injected iv over 90 sec. Arterial plasma and urine were analysed for unchanged F and for total ^{3}H (i.e., F and its metabolites).[1] Pharmacokinetic variables were calculated using non-linear, least squares regression analysis.

RESULTS. F elimination from plasma was described by the equation: $C_{p(t)} = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$. C_p represents F conc. at any time (t) after injection. The mean kinetic variables ± SEM for a 10 μg/kg dose in man are shown in the table along with data from dogs[1] for comparison. The rate constants were independent of dose and the intercepts proportional to dose. The initial decline of plasma F was rapid and attributable to its extensive uptake by tissues. Its apparent distribution volume (Vd) averaged 4 ± 0.3 L/kg and 57 ± 1% of F in plasma was bound to protein at pH 7.3 (respiratory acidosis). The half-time for the ultimate elimination of F was 3.6 ± 0.2 hrs; pharmacokinetic models of F disposition indicated that the rate-limiting step was its reuptake from certain peripheral tissues (e.g., fat). Biotransformation of F was efficient; metabolites were present in plasma 1.5 min after injection and accounted for 56% of total ^{3}H by 60 min. Urine collected over 72 hrs contained only 6 ± 1% of the dose as unchanged F and 70 ± 2% as metabolites.

DISCUSSION. The pharmacokinetics of F in awake volunteers were very similar to those reported for anesthetized dogs (table).[1] The extensive uptake of F by tissues (large Vd) and its prolonged elimination half-time indicate the potential for accumulation of F after large or repeated doses in man. It is likely that F accumulation will be associated with cumulative respiratory effects since there appears to be a close correlation between plasma levels of F and ventilatory depression in man (figure), and accumulation of both F and ventilatory depression has been demonstrated in the dog.[2] The anesthesiologist should be aware of this potential for prolonged ventilatory depression from this "short-acting" narcotic analgesic. He should also recognize that hypoventilation from residual F may recur when the intensity of noxious stimulation decreases (e.g., after surgery).

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REFERENCES.

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Table. Pharmacokinetics of Fentanyl in Plasma

	n	P ng/ml	π min^{-1}	A ng/ml	α min^{-1}	B ng/ml	β min^{-1}
Man	4	22.1 ±4.8	0.46 ±.05	3.0 ±.8	0.065 ±.008	2.2 ±.14	.0033 ±.0002
Dog	4	8.4 ±2.6	0.34 ±.03	2.4 ±.2	0.028 ±.003	0.60 ±.11	.0039 ±.0006

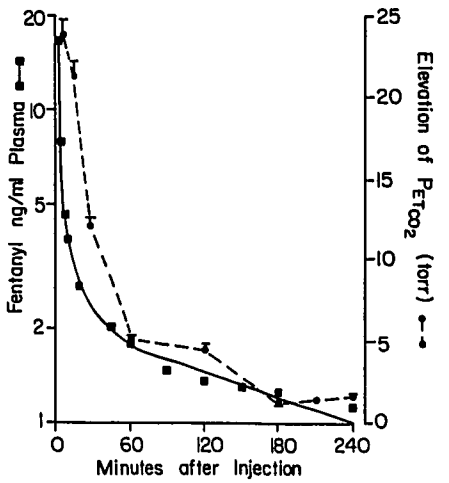

Fig. Comparison of fentanyl elimination from plasma and recovery from ventilatory depression in man. $P_{ET}CO_2$ values adapted from data of Harper et al.[3]